(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 160 578**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 85400270.6

(22) Date of filing: 15.02.85

(51) Int. Cl.⁴: C 07 D 471/04
//A61K31/435, C07D213/61,
C07D213/80, (C07D471/04,
221:00, 221:00)

(30) Priority: 17.02.84 JP 28278/84
19.03.84 JP 53159/84

(43) Date of publication of application:
06.11.85 Bulletin 85/45

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL SE

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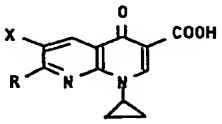
(54) **1,8-Naphthyridine derivatives.**

(57) Novel 1,8-naphthyridine derivatives having antibacterial activity and represented by the following general formula (I):



(I)

wherein:

R is a cyclic amino group which may have a substituent; and

X is a halogen atom,

and their pharmacologically acceptable salts and a process for their preparation are disclosed.

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1,8-NAPHTHYRIDINE DERIVATIVES

Field of the invention

The present invention relates to novel 1,8-naphthyridine derivatives presenting outstanding antibacterial activity as well as to their pharmacologically acceptable salts; it also relates to a process for their preparation.

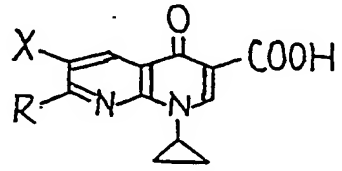
Description of the Prior Art

Japanese patent application n° 131346/82 filed on July 29, 1982 and laid open to public inspection on May 6, 1983 under Disclosure No. 74667/83 discloses bacteriocidal 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinoquinoline-3-carboxylic acids.

Furthermore, Japanese patent application No. 136 224/81 filed on September 1, 1981 and laid open to public inspection on May 15, 1982 under Disclosure No. 77683/82 discloses antibacterial 7-piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid compounds.

Brief summary of the invention

The present invention concerns novel 1,8-naphthyridine derivatives represented by the general formula (I):



(I)

wherein:

R is a cyclic substituent; and

X is a halogen atom,

and their pharmacologically acceptable salts, and a process for their

preparation. The 1,8-naphthyridine derivatives (I) and their pharmacologically acceptable salts are useful as antibacterial agents. The process comprises reacting 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid with one of the known cyclic amines. The 3-carboxylic acid is prepared from the known 2,6-dihydroxy-3-fluoropyridine-5-carboxamide or 2,6-dichloro-3-fluoropyridine-5-carbonitrile.

Thus, it is an object of the present invention to provide novel compounds presenting outstanding antibacterial activity.

Another object of the present invention is to provide a process for the preparation of these compounds.

These and other objects and advantages of the present invention will become apparent from reading through the following description.

Detailed description of the preferred embodiments

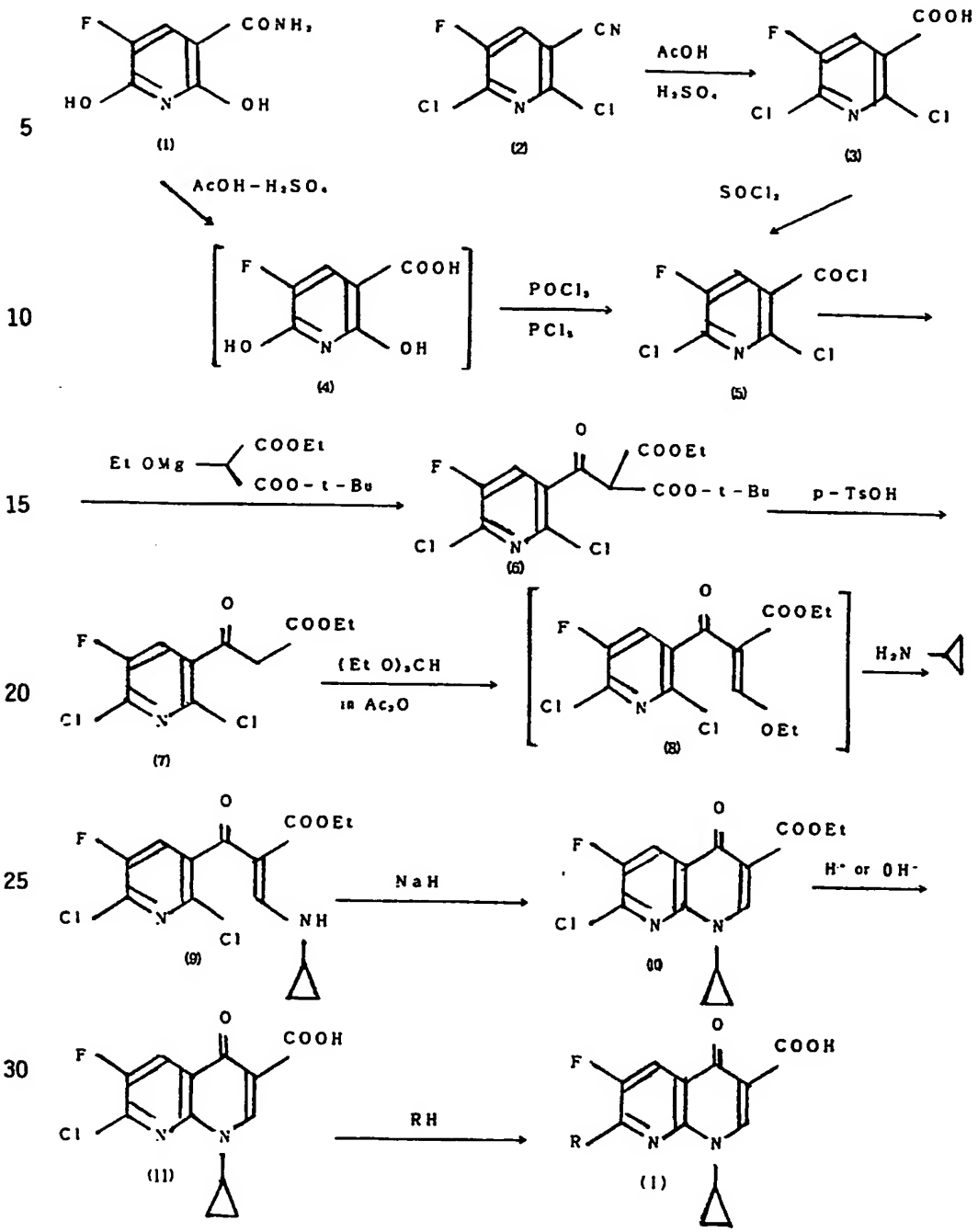
Throughout the specification and the claims the term "cyclic amino group which may have a substituent" used in the definition of group R includes, for example, 1-piperazinyl, 1-pyrrolidinyl or 1-homopiperazinyl group which may be substituted with a C_{1-7} alkyl, hydroxyl, acyl, amino, carbamoyl or cyano group. More particularly, R may be:

1-piperazinyl
3-amino-1-pyrrolidinyl
3-hydroxy-1-pyrrolidinyl
4-methyl-1-piperazinyl
1-homopiperazinyl
N-methyl-1-homopiperazinyl or
3-methyl-1-piperazinyl.

Embodiments of the term "pharmacologically acceptable salts" include salts with inorganic acids such as hydrochloric acid and sulfuric acid, with organic acids such as methanesulfonic acid, acetic acid and gluconic acid and with alkali or alkaline earth metals including sodium, potassium and calcium.

Compounds (I) may be in the form of hydrates.

The synthesis of the compounds of the present invention may be exemplified by the following reaction scheme:



In the above reaction scheme, the known 2,6-dihydroxy-3-fluoropyridine-5-carboxamide (1) is hydrolyzed with sulfuric acid-acetic acid to yield a carboxylic acid (4) which is, without further purification, treated

with phosphorus oxychloride-phosphorus pentachloride to produce 2,6-dichloro-3-fluoropyridine-5-carbonyl chloride (5). Alternatively, this acid chloride (5) can be obtained by hydrolyzing the known 2,6-dichloro-3-fluoropyridine-5-carbonitrile (2) to the corresponding carboxylic acid (3) followed by reflux of the latter in thionyl chloride and benzene. The acid chloride (5) is added to ethyl t-butyl ethoxy-magnesium-malonate, which is synthesized from ethoxy-magnesium ethoxide and ethyl t-butyl malonate, to yield ethyl t-butyl 2,6-dichloro-5-fluoronicotinoylmalonate (6) which is then refluxed with a catalytic amount of p-toluenesulfonic acid in benzene over a period of 3-5 hours to yield ethyl 2,6-dichloro-5-fluoronicotinoylacetate (7) (a mixture of keto and enol forms). This ester is reacted with ethyl orthoformate in acetic anhydride to produce ethyl 3-ethoxy-2-(2,6-dichloro-5-fluoronicotinoyl)-acrylate (8). This ester is then dissolved in dichloromethane without further purification. Cyclopropylamine at room temperature is added to the resulting solution to produce the corresponding 3-cyclopropylamino compound (9). This product is dissolved in anhydrous dioxane followed by addition of sodium hydride. The resulting mixture is then refluxed for 5-30 minutes and thereafter the product is purified by chromatography on silica gel. Thus, ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (10) is obtained. This compound (10) is converted to the corresponding carboxylic acid (11) by acid or alkaline hydrolysis and then reacted with a cyclic amine RH where R is defined as herein-above to produce the object compounds (I). Examples of the cyclic amine include, for example, piperazine, 3-t-butoxycarbonyl-aminopyrrolidine, 3-hydroxypyrrolidine, N-methylpiperazine, homopiperazine, N-methylhomopiperazine and 2-methylpiperazine. This reaction can be carried out in a solvent such as dimethylsulfoxide, dimethylformamide, pyridine or 3-methoxybutanol. The compounds (I) may be produced over 30 minutes to five hours at a temperature comprised between room temperature and 120°C, preferably at a temperature within the range of 40-100°C, and usually they may be produced from between 30 minutes and 2 hours. In the case where the cyclic amine is a protected one, such as 3-t-butoxycarbonylaminopyrrolidine, the protecting group such as 3-t-butoxycarbonyl may subsequently be conventionally eliminated.

The antibacterial activity of the compounds of the present invention was determined by the standard method of the Japan Society of

Chemotherapy: according to the dilution method in Muller-Hinton Bouillon, 10^6/ml of bacteria were seeded and incubated at 37°C for 18 hours. The results obtained by the method mentioned herein-above are summarized in the following table:

Table: Minimal Inhibitory Concentration (MIC) (μg/ml)

	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	Control Compound
E. coli, NIHJ	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	0.20
Sh. flexneri, 2a5503	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	0.10	≤0.05	0.20
Pr. vulgaris, 3167	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	0.10	≤0.05	0.20
Pr. mirabilis, 1287	≤0.05	≤0.05	≤0.05	≤0.05	0.10	0.20	0.10	0.20
Ser. marcescens, 13001	≤0.05	≤0.05	0.10	≤0.05	0.10	0.20	≤0.05	0.20
Ps. aeruginosa, 2063	0.10	≤0.05	0.39	0.39	0.20	0.78	0.20	0.78
Ps. aeruginosa, 2128	0.10	≤0.05	0.39	0.20	0.10	0.39	0.20	0.78
Ps. aeruginosa, 2131	0.10	0.10	0.78	0.39	0.20	0.78	0.10	0.20
Ps. cepacia, IID1340	3.13	0.39	0.39	1.56	0.78	0.78	0.39	50.0
Ps. maltophilia, IID1275	0.78	0.39	0.39	0.39	1.56	0.39	0.39	0.78
S. aureus, Smith	0.39	0.10	≤0.05	0.20	0.39	0.39	0.39	0.78
S. epidermis, 56556	0.39	0.10	0.10	0.39	0.39	0.39	0.78	0.78
Str. pyogenes, G-36	6.25	0.78	1.56	6.25	12.5	6.25	1.56	25.0
Str. faecalis, ATCC19433	1.56	0.39	0.39	3.13	6.25	6.25	3.13	6.25

No. 1: Compound of Example 1
No. 2: Compound of Example 2
No. 3: Compound of Example 3
No. 4: Compound of Example 4
No. 5: Compound of Example 5
No. 6: Compound of Example 6
No. 7: Compound of Example 7
Control compound:
1-ethyl-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (Example 2 of Japanese Patent Application Publication No. 10109/1982).

As shown in the above table, the antibacterial activity of the compounds of the present invention is superior to that of the control compound. Furthermore, they show significantly high oil solubility as compared with the corresponding quinoline derivatives, and, moreover, are expected to be satisfactorily absorbed through the intestinal tract and to show a high concentration in blood.

The compounds of the present invention are useful as antibacterial agents for the treatment of various infectious diseases such as urinary tract infections or infections in respiratory organs of mammals including humans. Normally these compounds are administered orally, but they can also be administered by injection or can be used by external application depending upon the type of disease to be treated.

Orally the compounds of the present invention can be administered at a dosage between 100 mg to 1000 mg, normally between 100 mg to 600 mg, per day for adults, in the form of various pharmaceutical preparations such as tablets, capsules, powders, granules, syrup and the like which are well known in the prior art. Preparations of compounds of the present invention suitable for injection or external application can also be prepared by techniques known in the art. For example, they can be prepared by methods known per se using suitable diluents, binders, excipients, disintegrators, coating agents and the like.

The acute toxicity of the compounds of the present invention (I) was 200 or more mg/kg in mice (i.v.).

The present invention will be explained herein-below in more detail with reference to the Reference Example and Examples given below. Unless otherwise indicated, all parts, percents, ratios and the like are by weight.

Reference Example

(a) 12 g of 2,6-dichloro-3-fluoropyridine-5-carbonitrile (2) was added to a mixture of 60 ml of acetic acid, 5.8 ml of water and 5.8 ml of conc. sulfuric acid followed by reflux for 16 hours. After the reaction, 200 ml of water was added to the reaction mixture which was then submitted to 3 successive extractions with 150 ml portions of ethyl acetate. The extracts were washed with 100 ml of a saturated aqueous saline solution, dried over sodium sulfate, and the solvent was distilled off to yield 6.8 g of 2,6-dichloro-3-fluoro-pyridine-5-carboxylic acid (3) as crystalline powders:

NMR: $CDCl_3$

δ ppm

8.10 (1H, d, J = 8.0 Hz, aromatic H)

9.92 (1H, broad S, -COOH)

(b) 5 ml of thionyl chloride and 60 ml of benzene were added to 3.9 g of the carboxylic acid (3) from step (a), and the resulting mixture was refluxed for 1 hour. Thereafter, the mixture was cooled, the solvent was distilled off, and then benzene was added to the resulting residue followed by stirring. The mixture was subjected to two successive treatments for removing the supernatant benzene to yield an acid chloride (5) as an oily material. This material was dissolved in 20 ml of ether and then the resulting solution was gradually added dropwise to another solution which was separately prepared by refluxing 3.67 g of ethyl t-butyl malonate and 2.2 g of magnesium ethoxide in 40 ml of ether for 1 hour and then cooling the mixture to room temperature. After the addition, the resulting mixture was refluxed for 15 minutes, and then the solution was allowed to cool to room temperature followed by addition of water thereto. The pH of the solution was adjusted to lower than 4 with sulfuric acid, and it was partitioned with ether. The aqueous layer was then submitted to three successive extractions with 100 ml portions of ether. The combined ether extracts were washed with a saturated aqueous saline solution and dried over sodium sulfate. The removal of the ether gave 3.4 g of ethyl t-butyl 2,6-dichloro-5-fluoronicotinoyl-malonate (6) as an oily material.

NMR: $CDCl_3$

δ ppm

1.48, 1.58 (two t-butyls)

7.49 (1H, d, pyridine H)

(c) 3.1 g of 2,6-dihydroxy-3-fluoropyridine-5-carboxamide (1) (or 2,6-dihydroxy-5-fluoronicotinamide) was added to a mixture of 10 ml of acetic acid, 1 ml of water and 4 ml of sulfuric acid, and the resulting mixture was refluxed for 24 hours. Thereafter the mixture was cooled and the solvent was distilled off under reduced pressure, 10 ml of ice water was added to the residue, and the mixture was neutralized by addition of sodium bicarbonate thereto and then extracted with excess chloroform. After drying over sodium sulfate the solvent was distilled off, and the residue was,

without further purification, added to a mixture of 5 ml of phosphorus oxychloride and 1 g of phosphorus pentachloride. The resulting mixture was refluxed for 3 hours and then cooled, and thereafter the solvent was distilled off under reduced pressure. The resulting residue was stirred after addition of 20 ml of benzene thereto and then subjected to three successive treatments for removing the supernatant benzene to yield 2.2 g of 2,6-dichloro-3-fluoropyridine-5-carbonyl chloride (5).

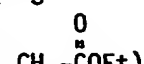
(d) 150 mg of p-toluenesulfonic acid and 100 ml of dry benzene were added to 3.4 g of ethyl t-butyl 2,6-dichloro-5-fluoronicotinoyl-malonate (6). The resulting mixture was refluxed for 3 hours, and then the solvent was distilled off under reduced pressure. The residue was purified by chromatography on silica gel (50 g). Thus, 2.3 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (7) was obtained from the benzene extracts.

NMR: $CDCl_3$

δ ppm

1.35 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)

4.28 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$)

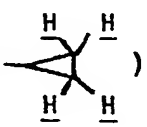
4.08 & 5.80 (enol) 2H ()

7.78 (1H, d, J = 8 Hz, pyridine $\underline{H}$)

(e) 1.3 g of ethyl orthoformate and 40 ml of acetic anhydride were added to 2.2 g of the β-keto ester (7) from the step (d), and the mixture was heated to reflux for 15 minutes. Then the solvent was distilled off and 30 ml of dichloromethane was added to the crude ethoxymethylene compound (8) thus obtained. To the resulting mixture under cooling with ice and stirring was added dropwise 5 ml of a solution of 500 mg of cyclopropylamine in dichloro-methane. The mixture was stirred for 20 minutes at room temperature, and the solvent was distilled off. The resulting residue was purified by chromatography on silica gel (20 g) (eluant 3%-ethyl acetate/benzene 20 g) to give 1.3 g of ethyl 3-cyclopropylamino-2-(2,6-dichloro-5-fluoronicotinoyl)-acrylate (9).

NMR: $CDCl_3$

δ ppm

0.8 - 1.0 (4H, m, )

1.06 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)

3.00 (1H, m, $>N-$ )

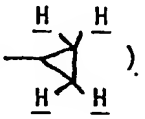
4.02 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$)

8.21 (1H, d, J = 13 Hz, pyridine $\underline{H}$)

(f) 690 mg of the compound (9) from the step (e) was added to 20 ml of a suspension of 105 mg of sodium hydride (50% dispersion in oil) in dioxane, and the mixture was refluxed for 10 minutes. The reaction solution was red colored. The solution was allowed to cool to room temperature, poured into 50 ml of ice water and then made acidic (pH < 3) with dilute hydrochloric acid. The mixture was extracted with three portions each of 50 ml of chloroform and dried over sodium sulfate, and then the residue was purified through a column of silica gel (10 g). Thus, ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (10) was obtained as chloroform extracts. Recrystallization from ethanol gave 270 mg of colorless needles of the compound (10) (mp.: 175-176.5°C).

NMR: $CDCl_3$

δ ppm

0.9 - 1.4 (4H, m, $>N-$ )

1.40 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)

3.64 (1H, m, $-N-$ )

4.40 (2H, q, J = 7 Hz, $-\underline{CH_2}CH_3$)

8.82 (1H, d, J = 8 Hz, aromatic $C_5-\underline{H}$)

8.64 (1H, s, $C_2-\underline{H}$)

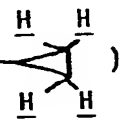
Analysis ($C_{14}H_{12}ClFN_2O_3$):

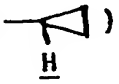
	C	H	N
- calculated	54.12	3.89	9.01
- found	54.31	3.87	9.00

(g) 350 mg of the ester (8) from the step (f) was added to 20 ml of a mixture of acetic acid and hydrochloric acid (1:1), and the resulting mixture was refluxed for 1.5 hours. The reaction mixture was concentrated under reduced pressure to between 5 and 10 ml and 20 ml of water was added to the concentrate. The crystals were collected by filtration and washed successively with water, ethanol and ether. Recrystallization from ethanol gave 240 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11) melting at 223-224°C.

NMR: $CDCl_3$

δ ppm

1.0 - 1.4 (4H, m, )

3.8 - 3.95 (1H, m, )

8.48 (1H, d, J = 8 Hz, C_5-H)

8.96 (1H, s, C_2-H)

Analysis ($C_{12}H_8FClN_2O_3 \cdot 1/4\ H_2O$)

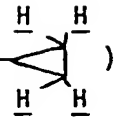
	C	H	N
- calculated	50.19	2.98	9.75
- found	50.13	3.18	9.50

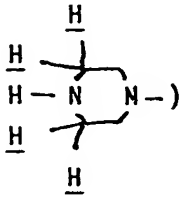
EXAMPLE 1

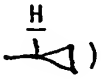
150 mg of anhydrous piperazine and 6 ml of pyridine were added to 100 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11), and the mixture was heated at 60°C for 30 minutes while stirring. After the reaction the solvent was distilled off under reduced pressure, and ethanol was added to the residue to produce crystallization. The crystals were collected by filtration and washed with ethanol. After being dried, the crystals were dissolved in an ethanol-aqueous ammonia mixture. 100 mg of activated carbon was added to the mixture followed by filtration. The filtrate was concentrated, and the crystals were collected by filtration and dried to give 95 mg of 1-cyclopropyl-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid {mp.: 251-256°C (dec.)}.

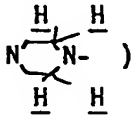
NMR: $CDCl_3$

δ ppm

1.0 - 1.3 (4H, m, )

2.8 - 3.0 (4H, m, )

3.6 - 3.8 (1H, m, )

3.7 - 3.9 (4H, m, )

8.06 (1H, d, J = 14 Hz, aromatic C_6-H)

8.62 (1H, s, C_2-H)

Analysis ($C_{16}H_{17}FN_4O_3$)

	C	H	N
- calculated	57.82	5.15	16.86
- found	57.68	5.22	16.52

EXAMPLE 2

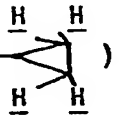
200 mg of 3-t-butoxycarbonylaminopyrrolidine and 8 ml of pyridine were added to 150 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11). The mixture was heated at 60°C for 30 minutes while stirring. Then the solvent was distilled off, and ethanol was added to the residue to produce crystallization. The crystals were collected by filtration and washed thoroughly with ethanol and then with ether to give a 7-(3-t-butoxycarbonylamino-1-pyrrolidinyl)compound.

Without further purification this product was added to a mixture of 10 ml of trifluoroacetic acid and 200 mg of anisole followed by stirring at room temperature for 1 hour. Thereafter, the solvent was distilled off under reduced pressure, and the residue was neutralized with

methanol-aqueous sodium bicarbonate added thereto. The crystals were collected by filtration and washed thoroughly with ethanol and then with ether followed by drying. The crystals were dissolved in 10 ml of conc. aqueous ammonia. 100 mg of activated carbon was added to the mixture followed by filtration. The filtrate was concentrated, and thus 90 mg of 1-cyclopropyl-6-fluoro-7-(3-amino-1-pyrrolidinyl)-1,4-dihydro-4-oxo-1,8--naphthyridine-3-carboxylic acid {mp.: 243-248°C (dec.)} as colorless needles was obtained.

NMR: DMSO-d_6

δ ppm

1.0 - 1.3 (4H, m, )

7.96 (1H, d, J = 14 Hz, C_5-H)

8.58 (1H, s, C_2-H)

Analysis ($C_{16}H_{17}FN_4O_3$)

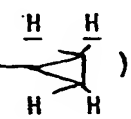
	C	H	N
- calculated	57.82	5.15	16.86
- found	57.53	5.26	16.76

EXAMPLE 3

150 mg of 3-hydroxypyrrolidine and 10 ml of pyridine were added to 100 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11) and the reaction was carried out at 60°C for 30 minutes. The solvent was distilled off under reduced pressure, and ethanol was added to the residue to produce crystallization. The crystals were collected by filtration and washed thoroughly with ethanol and then with ether followed by drying. The crystals were dissolved in an ethanol-aqueous ammonia mixture and then treated with activated carbon. After filtration the mother liquor was concentrated by heating, and the separated crystals were collected by filtration and dried to give 95 mg of 1-cyclopropyl-6-fluoro-7-(3-hydroxy-1-pyrrolidinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (mp.: 300°C).

NMR: DMSO-d_6

δ ppm

1.0 - 1.4 (4H, m, )

7.95 (1H, d, J = 14 Hz, C_5-H)

8.56 (1H, s, C_2-H)

Analysis ($C_{16}H_{16}FN_3O_4 \cdot 1/4\ H_2O$)

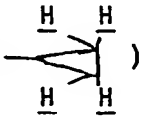
	C	H	N
- calculated	56.89	4.92	12.43
- found	57.06	4.78	12.46

EXAMPLE 4

150 mg of N-methylpiperazine and 10 ml of pyridine were added to 100 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11) and the mixture was heated at 60°C for 1 hour while stirring. After the reaction the solvent was distilled off under reduced pressure, and the residue was washed thoroughly with ethanol and then with ether and then dried. The resulting crystals were dissolved in an ethanol-aqueous ammonia mixture. To the solution there was added activated carbon followed by filtration. The filtrate was concentrated by heating, and the crystals were collected by filtration to give 100 mg of light yellow crystals of 1-cyclopropyl-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid {mp.: 244-245°C (dec.)}.

NMR: DMSO-d_6

δ ppm

1.0 - 1.3 (4H, m, >N- )

8.06 (1H, d, J = 14 Hz, C_5-H)

2.24 (3H, s, CH_3-N N-)

Analysis ($C_{17}H_{19}FN_3O_4$)

	C	H	N
- calculated	58.95	5.52	16.18
- found	59.08	5.58	16.18

EXAMPLE 5

150 mg of homopiperazine and 5 ml of pyridine were added to 70 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11) and the mixture was stirred at 80°C for 1 hour.

After the reaction the solvent was distilled off under reduced pressure, and the residue was washed successively with two portions each of small amounts of water, ethanol and ether, and then dried. The resulting crystals were dissolved in 10 ml of ethanol followed by addition of excess conc. ammonia. The solution was treated with activated carbon and then filtered. The resulting filtrate was concentrated by heating, and the crystals were collected by filtration and dried to give 70 mg of 1-cyclopropyl-6-fluoro-7-(1-homopiperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid {mp.: 246-247°C (dec.)}.

Analysis ($C_{17}H_{19}FN_4O_3$)

	C	H	N
- calculated	58.95	5.53	16.18
- found	58.85	5.57	16.10

EXAMPLE 6

150 mg of N-methylhomopiperazine and 10 ml of pyridine were added to 100 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11) and the mixture was stirred at 60°C for 1 hour. After being cooled, the solvent was distilled off under reduced pressure, and the residue was washed successively with two portions each of small amounts of water and ethanol-ether (1:4). After being dried, the resulting light yellow powders were dissolved in ethanol-aqueous ammonia and then treated with activated carbon followed by filtration. The filtrate was concentrated by heating, and the crystals were collected by filtration and dried. 90 mg of 1-cyclopropyl-6-fluoro-7-(N-methyl-1-homopiperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid {mp.: 247-257°C (dec., unclear)} were thus obtained.

Analysis ($C_{18}H_{21}FH_4O_3$)

	C	H	N
- calculated	59.99	5.87	15.55
- found	59.67	5.78	15.55

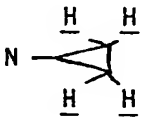
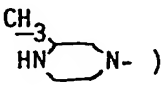
EXAMPLE 7

130 mg of 2-methylpiperazine and 5 ml of pyridine were added to 100 mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11) and the mixture was stirred at an external temperature of 60°C for 30 minutes. Then the solvent was distilled off under reduced pressure, and 2 ml of ethanol was added to

the residue to produce crystallization. The crystals were collected by filtration and washed successively with ethanol and ether. After being dried, the resulting crude crystals were suspended in 10 ml of ethanol and then dissolved therein by addition of excess conc. aqueous ammonia and then treated with activated carbon. The mixture was concentrated to remove the ammonia thereby giving as transparent crystals 40 mg of 1-cyclopropyl-6-fluoro-7-(3-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-1,8--naphthyridine-3-carboxylic acid (mp.: 236-239°C).

NMR: DMSO-d_6

δ ppm

1.0 - 1.4 (7H, m,  & )

2.7 - 4.6 (7H, m, piperazine H)

8.06 (1H, d, J = 14 Hz, C_5-H)

8.62 (1H, s, C_2-H)

Analysis ($C_{17}H_{19}FN_4O_3$)

	C	H	N
- calculated	58.95	5.52	16.18
- found	58.66	5.78	15.91

The following is an example of preparations for oral administration containing the compounds of the present invention (I).

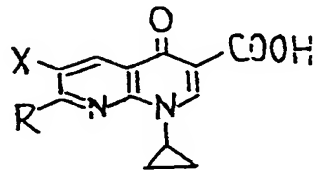
Capsules

. compound (I)	100.0 mg
. corn starch	23.0 mg
. CMC calcium	22.5 mg
. hydroxypropylmethyl cellulose	3.0 mg
. magnesium stearate	1.5 mg

Total	150.0 mg per capsule

CLAIMS

1.- 1,8-naphthyridine derivatives represented by the following general formula:



(I)

wherein:

R is a cyclic amino group which may have a substituent; and

X is a halogen atom,

and their pharmacologically acceptable salts.

2.- 1,8-naphthyridine derivatives as claimed in claim 1, wherein R is a 5, 6 or 7 -membered cyclic amino group comprising one or two nitrogen atoms and which may have a substituent.

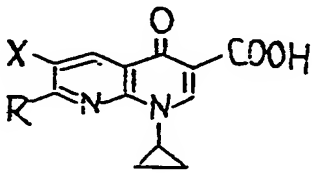
3.- 1,8-naphthyridine derivatives as claimed in claim 1 or 2, wherein R is piperazinyl, pyrrolidinyl or homopiperazinyl which may have a substituent.

4.- 1,8-naphthyridine derivatives as claimed in claim 1, 2 or 3, wherein the substituent is selected from the group consisting of C_{1-6} alkyl, hydroxyl, acyl, amino, carbamoyl and cyano groups.

5.- 1,8-naphthyridine derivatives as claimed in claim 1, 2, 3 or 4, wherein R is 3-methyl-1-piperazinyl.

6.- 1,8-naphthyridine derivatives as claimed in claim 1, 2 or 4, wherein R is 1-piperazinyl.

7.- A process for the preparation of 1,8-naphthyridine derivatives represented by the following general formula:



wherein:

R is a cyclic amino group which may have a substituent; and

X is a halogen atom,

which comprises reacting 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid with a cyclic amine: RH wherein R is defined as the above.

European Patent Office

EUROPEAN SEARCH REPORT

0160578
Application number

EP 85 40 0270

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
D,Y	EP-A-0 049 355 (BAYER) * Claim 1 * & JP - A - 81 136 224	1	C 07 D 471/04 // A 61 K 31/435 C 07 D 213/61 C 07 D 213/80 (C 07 D 471/04 C 07 D 221:00 C 07 D 221:00)
Y	FR-A-2 500 833 (ROGER BELLON) * Claim 1 *	1	
D,Y	EP-A-0 078 362 (BAYER) * Claim 1 *	1	
P,X	EP-A-0 106 489 (WARNER-LAMBERT) * Claim 1 *	1	
P,X	EP-A-0 132 845 (DAINIPPON) * Claim 1 *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 471/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28-06-1985	ALFARO I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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